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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/674,159

09/29/2003

Jianzhu Chen

0492611-0506 (MIT 9926)

1899

24280 7590 08/20/2009  
CHOATE, HALL & STEWART LLP  
TWO INTERNATIONAL PLACE  
BOSTON, MA 02110

EXAMINER

MCGARRY, SEAN

ART UNIT

PAPER NUMBER

1635

NOTIFICATION DATE

DELIVERY MODE

08/20/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/674,159	<b>Applicant(s)</b> CHEN ET AL.	
	<b>Examiner</b> Sean R. McGarry	<b>Art Unit</b> 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 24 June 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-22,26-35,39-174 and 177-201 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-20,22,27,28,31-35,70-88,90-93,98-104,112-117,145,165-174,177,178 and 185-193 is/are rejected.
- 7) ☒ Claim(s) 39-48,64-69,94-97,179-184 and 201 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                        |                                                                   |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/24/09</u> .                                                 | 6) <input type="checkbox"/> Other: _____                          |

Continuation of Disposition of Claims: Claims withdrawn from consideration are 21,29,30,49-63,89,105-111,118-144,146-164 and 194-200.

## **DETAILED ACTION**

This Official Action is in response to the response filed 6/24/09. Any rejections or objections made in the previous Official Action and not repeated herein are withdrawn.

### ***Specification***

The disclosure is objected to because of the following informalities: Page 84 of the specification is blank.

Appropriate correction is required. Applicant has asserted that page 84 was provided at the time of filing and directs the examiner to paragraphs 265-266 of the published application. The examiner acknowledges that it appears that page 84 was provided at the time of filing, however the specification and the application file now lacks page 84. Applicant should provide a replacement page 84 so that any patent that may issue from this application may be issued.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20, 22, 27, 28, 31-35, 70-88, 90-93, 98-104, 112-117, 145, 165-174, 177, 178 and 185-193 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al [US 2004/0259,247] and Beach et al [US 2002/0162126, cited by applicant] in view of Abe et al [European Journal of Pharmaceutical Sciences, Vol. 13:61-69, 2001, cited by applicant], Gitlin et al. [Nature Vol.418:430-434, 25 July 2002, cited by applicant], Brummelkamp et al [Science Vol. 296:550-553, 19 April 2002, cited by applicant], and Paddison et al [Genes & Development Vol.16:948-958, 2002].

The invention is as clearly set forth in the claims.

Tuschl et al have taught the use of siRNA and have taught that siRNA may be used to inhibit viral genes. Tuschl teaches, for example:

[0008] The object underlying the present invention is to provide novel agents capable of mediating target-specific RNA interference or other target-specific nucleic acid modifications such as DNA methylation, said agents having an improved efficacy and safety compared to prior art agents.

[0009] The solution of this problem is provided by an isolated double-stranded RNA molecule, wherein each RNA strand has a length from 19-25, particularly from 19-23 nucleotides, wherein

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said RNA molecule is capable of mediating target-specific nucleic acid modifications, particularly RNA interference and/or DNA methylation. Preferably at least one strand has a 3'-overhang from 1-5 nucleotides, more preferably from 1-3 nucleotides and most preferably 2 nucleotides. The other strand may be blunt-ended or has up to 6 nucleotides 3' overhang. Also, if both strands of the dsRNA are exactly 21 or 22 nt, it is possible to observe some RNA interference when both ends are blunt (0 nt overhang). The RNA molecule is preferably a synthetic RNA molecule which is substantially free from contaminants occurring in cell extracts, e.g. from *Drosophila* embryos. Further, the RNA molecule is preferably substantially free from any non-target-specific contaminants, particularly non-target-specific RNA molecules e.g. from contaminants occurring in cell extracts.

[0010] Further, the invention relates to the use of isolated double-stranded RNA molecules, wherein each RNA strand has a length from 19-25 nucleotides, for mediating, target-specific nucleic acid modifications, particularly RNAi, in mammalian cells, particularly in human cells.

[0011] Surprisingly, it was found that synthetic short double-stranded RNA molecules particularly with overhanging 3'-ends are sequence-specific mediators of RNAi and mediate efficient target-RNA cleavage, wherein the cleavage site is located near the center of the region spanned by the guiding short RNA.

[0012] Preferably, each strand of the RNA molecule has a length from 20-22 nucleotides (or 20-25 nucleotides in mammalian cells), wherein the length of each strand may be the same or different. Preferably, the length of the 3'-overhang reaches from 1-3 nucleotides, wherein the length of the overhang may be the same or different for each strand. The RNA-strands preferably have 3'-hydroxyl groups. The 5'-terminus preferably comprises a phosphate, diphosphate, triphosphate or hydroxyl group. The most effective dsRNAs are composed of two 21 nt strands which are paired such that 1-3, particularly 2 nt 3' overhangs are present on both ends of the dsRNA.

[0013] The target RNA cleavage reaction guided by siRNAs is highly sequence-specific. However, not all positions of a siRNA contribute equally to target recognition. Mismatches in the center of the siRNA duplex are most critical and essentially abolish target RNA cleavage. In contrast, the 3' nucleotide of the siRNA strand (e.g. position 21) that is complementary to the single-stranded target RNA, does not contribute to specificity of the target recognition. Further, the sequence of the unpaired 2-nt 3' overhang of the siRNA strand with the same polarity as the target RNA is not critical for target RNA cleavage as only the antisense siRNA strand guides target recognition. Thus, from the single-stranded overhanging nucleotides only the penultimate position of the antisense siRNA (e.g. position 20) needs to match the targeted sense mRNA.

[0014] Surprisingly, the double-stranded RNA molecules of the present invention exhibit a high in vivo stability in serum or in growth medium for cell cultures. In order to further enhance the stability, the 3'-overhangs may be stabilized against degradation, e.g. they may be selected such that they consist of purine nucleotides, particularly adenosine or guanosine nucleotides. Alternatively, substitution of pyrimidine nucleotides by modified analogues, e.g. substitution of uridine 2 nt 3' overhangs by 2'-deoxythymidine is tolerated and does not affect the efficiency of

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RNA interference. The absence of a 2' hydroxyl significantly enhances the nuclease resistance of the overhang in tissue culture medium.

[0015] In an especially preferred embodiment of the present invention the RNA molecule may contain at least one modified nucleotide analogue. The nucleotide analogues may be located at positions where the target-specific activity, e.g. the RNAi mediating activity is not substantially effected, e.g. in a region at the 5'-end and/or the 3'-end of the double-stranded RNA molecule. Particularly, the overhangs may be stabilized by incorporating modified nucleotide analogues.

[0016] Preferred nucleotide analogues are selected from sugar- or backbone-modified ribonucleotides. It should be noted, however, that also nucleobase-modified ribonucleotides, i.e. ribonucleotides, containing a non-naturally occurring nucleobase instead of a naturally occurring nucleobase such as uridines or cytidines modified at the 5-position, e.g. 5-(2-amino)propyl uridine, 5-bromo uridine; adenosines and guanosines modified at the 8-position, e.g. 8-bromo guanosine; deaza nucleotides, e.g. 7-deaza-adenosine; O- and N-alkylated nucleotides, e.g. N6-methyl adenosine are suitable. In preferred sugar-modified ribonucleotides the 2'OH-group is replaced by a group selected from H, OR, R, halo, SH, SR, NH.sub.2, NHR, NR.sub.2 or CN, wherein R is C.sub.1-C.sub.6 alkyl, alkenyl or alkynyl and halo is F, Cl, Br or I. In preferred backbone-modified ribonucleotides the phosphoester group connecting to adjacent ribonucleotides is replaced by a modified group, e.g. of phosphothioate group. It should be noted that the above modifications may be combined.

[0017] The sequence of the double-stranded RNA molecule of the present invention has to have a sufficient identity to a nucleic acid target molecule in order to mediate target-specific RNAi and/or DNA methylation. Preferably, the sequence has an identity of at least 50%, particularly of at least 70% to the desired target molecule in the double-stranded portion of the RNA molecule. More preferably, the identity is at least 85% and most preferably 100% in the double-stranded portion of the RNA molecule. The identity of a double-stranded RNA molecule to a predetermined nucleic acid target molecule, e.g. an mRNA target molecule may be determined as follows:  $100 \cdot \frac{I}{L}$

[0020] The double-stranded RNA molecule of the invention may be prepared by a method comprising the steps:

[0021] (a) synthesizing two RNA strands each having a length from 19-25, e.g. from 19-23 nucleotides, wherein said RNA strands are capable of forming a double-stranded RNA molecule, wherein preferably at least one strand has a 3'-overhang from 1-5 nucleotides,

[0022] (b) combining the synthesized RNA strands under conditions, wherein a double-stranded RNA molecule is formed, which is capable of mediating target-specific nucleic acid modifications, particularly RNA interference and/or DNA methylation.

[0028] Preferably the contacting step (a) comprises introducing the double-stranded RNA molecule into a target cell, e.g. an isolated target cell, e.g. in cell culture, a unicellular

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microorganism or a target cell or a plurality of target cells within a multicellular organism. More preferably, the introducing step comprises a carrier-mediated delivery, e.g. by liposomal carriers or by injection.

[0030] The target gene to which the RNA molecule of the invention is directed may be associated with a pathological condition. For example, the gene may be a pathogen-associated gene, e.g. a viral gene, a tumor-associated gene or an autoimmune disease-associated gene. The target gene may also be a heterologous gene expressed in a recombinant cell or a genetically altered organism. By determining or modulating, particularly, inhibiting the function of such a gene valuable information and therapeutic benefits in the agricultural field or in the medicine or veterinary medicine field may be obtained.

[0031] The dsRNA is usually administered as a pharmaceutical composition. The administration may be carried out by known methods, wherein a nucleic acid is introduced into a desired target cell in vitro or in vivo. Commonly used gene transfer techniques include calcium phosphate, DEAE-dextran, electroporation and microinjection and viral methods (Graham, F. L. and van der Eb, A. J. (1973) *Viol.* 52, 456; McCutchan, J. H. and Pagano, J. S. (1968), *J. Natl. Cancer Inst.* 41, 351; Chu, G. et al (1987), *Nucl. Acids Res.* 15, 1311; Fraley, R. et al. (1980), *J. Biol. Chem.* 255, 10431; Capecchi, M. R. (1980), *Cell* 22, 479). A recent addition to this arsenal of techniques for the introduction of DNA into cells is the use of cationic liposomes (Feigner, P. L. et al. (1987), *Proc. Natl. Acad. Sci USA* 84, 7413). Commercially available cationic lipid formulations are e.g. Tfx 50 (Promega) or Lipofectamin 2000 (Life Technologies).

[0032] Thus, the invention also relates to a pharmaceutical composition containing as an active agent at least one double-stranded RNA molecule as described above and a pharmaceutical carrier. The composition may be used for diagnostic and for therapeutic applications in human medicine or in veterinary medicine.

[0033] For diagnostic or therapeutic applications, the composition may be in form of a solution, e.g. an injectable solution, a cream, ointment, tablet, suspension or the like. The composition may be administered in any suitable way, e.g. by injection, by oral, topical, nasal, rectal application etc. The carrier may be any suitable pharmaceutical carrier. Preferably, a carrier is used, which is capable of increasing the efficacy of the RNA molecules to enter the target-cells. Suitable examples of such carriers are liposomes, particularly cationic liposomes. A further preferred administration method is injection.

[0035] Thus, a further subject matter of the invention is a eukaryotic cell or a eukaryotic non-human organism exhibiting a target gene-specific knockout phenotype comprising an at least partially deficient expression of at least one endogenous target gene wherein said cell or organism is transfected with at least one double-stranded RNA molecule capable of inhibiting the expression of at least one endogenous target gene or with a DNA encoding at least one double stranded RNA molecule capable of inhibiting the expression of at least one endogenous target gene. It should be noted that the present invention allows a target-specific knockout of several different endogenous genes due to the specificity of RNAi.



Beach et al also teach siRNA and teach shRNA compounds that may be expressed from a vector. Beach teaches, for example:

[0014] In certain preferred embodiments, the target gene is an endogenous gene of the cell. In other embodiments, the target gene is an heterologous gene relative to the genome of the cell, such as a pathogen gene, e.g., a viral gene.

[0017] In certain preferred embodiments, the length of the dsRNA is at least 20, 21 or 22 nucleotides in length, e.g., corresponding in size to RNA products produced by Dicer-dependent cleavage. In certain embodiments, the dsRNA construct is at least 25, 50, 100, 200, 300 or 400 bases. In certain embodiments, the dsRNA construct is 400-800 bases in length.

[0018] In certain preferred embodiments, expression of the target gene is attenuated by at least 5 fold, and more preferably at least 10, 20 or even 50 fold, e.g., relative to the untreated cell or a cell treated with a dsRNA construct which does not correspond to the target gene. Tuschl and beach et al do not teach specifically targeting influenza or the np gene of influenza. They do not specifically teach targeting conserved regions of a viral gene, for example.

[0037] The dsRNA construct may comprise one or more strands of polymerized ribonucleotide. It may include modifications to either the phosphate-sugar backbone or the nucleoside. The double-stranded structure may be formed by a single self-complementary RNA strand or two complementary RNA strands. RNA duplex formation may be initiated either inside or outside the cell. The dsRNA construct may be introduced in an amount which allows delivery of at least one copy per cell. Higher doses of double-stranded material may yield more effective inhibition. Inhibition is sequence-specific in that nucleotide sequences corresponding to the duplex region of the RNA are targeted for genetic inhibition. dsRNA constructs containing a nucleotide sequences identical to a portion of the target gene is preferred for inhibition. RNA sequences with insertions, deletions, and single point mutations relative to the target sequence have also been found to be effective for inhibition. Thus, sequence identity may be optimized by alignment algorithms known in the art and calculating the percent difference between the nucleotide sequences. Alternatively, the duplex region of the RNA may be defined functionally as a nucleotide sequence that is capable of hybridizing with a portion of the target gene transcript.

[0084] As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to that it has been linked. One type of vector is a genomic integrated vector, or "integrated vector", which can become integrated into the chromosomal DNA of the host cell. Another type of vector is an episomal vector, i.e., a nucleic acid capable of extra-chromosomal replication. Vectors capable of directing the expression of genes to that they are operatively linked are referred to herein as "expression vectors". In the present specification, "plasmid" and "vector" are used interchangeably unless otherwise clear from the context.

[0120] The cell with the target gene may be derived from or contained in any organism (e.g., plant, animal, protozoan, virus, bacterium, or fungus). The dsRNA construct may be synthesized either in vivo or in vitro. Endogenous RNA polymerase of the cell may mediate transcription in vivo, or cloned RNA polymerase can be used for transcription in vivo or in vitro. For generating

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double stranded transcripts from a transgene in vivo, a regulatory region may be used to transcribe the RNA strand (or strands).

[0122] The cell with the target gene may be derived from or contained in any organism. The organism may be a plant, animal, protozoan, bacterium, virus, or fungus. The plant may be a monocot, dicot or gymnosperm; the animal may be a vertebrate or invertebrate. Preferred microbes are those used in agriculture or by industry, and those that are pathogenic for plants or animals. Fungi include organisms in both the mold and yeast morphologies.

[0128] The target gene may be a gene derived from the cell, an endogenous gene, a transgene, or a gene of a pathogen which is present in the cell after infection thereof. Depending on the particular target gene and the dose of double stranded RNA material delivered, the procedure may provide partial or complete loss of function for the target gene. Lower doses of injected material and longer times after administration of dsRNA may result in inhibition in a smaller fraction of cells. Quantitation of gene expression in a cell may show similar amounts of inhibition at the level of accumulation of target mRNA or translation of target protein.

[0133] The dsRNA construct may comprise one or more strands of polymerized ribonucleotide. It may include modifications to either the phosphate-sugar backbone or the nucleoside. For example, the phosphodiester linkages of natural RNA may be modified to include at least one of a nitrogen or sulfur heteroatom. Modifications in RNA structure may be tailored to allow specific genetic inhibition while avoiding a general panic response in some organisms which is generated by dsRNA. Likewise, bases may be modified to block the activity of adenosine deaminase. The dsRNA construct may be produced enzymatically or by partial/total organic synthesis, any modified ribonucleotide can be introduced by in vitro enzymatic or organic synthesis.

[0135] The double-stranded structure may be formed by a single self-complementary RNA strand or two complementary RNA strands. RNA duplex formation may be initiated either inside or outside the cell. The RNA may be introduced in an amount which allows delivery of at least one copy per cell. Higher doses (e.g., at least 5, 10, 100, 500 or 1000 copies per cell) of double-stranded material may yield more effective inhibition; lower doses may also be useful for specific applications. Inhibition is sequence-specific in that nucleotide sequences corresponding to the duplex region of the RNA are targeted for genetic inhibition.

[0137] 100% sequence identity between the RNA and the target gene is not required to practice the present invention. Thus the invention has the advantage of being able to tolerate sequence variations that might be expected due to genetic mutation, strain polymorphism, or evolutionary divergence.

[0138] The dsRNA construct may be synthesized either in vivo or in vitro. Endogenous RNA polymerase of the cell may mediate transcription in vivo, or cloned RNA polymerase can be used for transcription in vivo or in vitro. For transcription from a transgene in vivo or an expression construct, a regulatory region (e.g., promoter, enhancer, silencer, splice donor and acceptor, polyadenylation) may be used to transcribe the dsRNA strand (or strands). Inhibition may be targeted by specific transcription in an organ, tissue, or cell type; stimulation of an environmental

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condition (e.g., infection, stress, temperature, chemical inducers); and/or engineering transcription at a developmental stage or age. The RNA strands may or may not be polyadenylated; the RNA strands may or may not be capable of being translated into a polypeptide by a cell's translational apparatus. The dsRNA construct may be chemically or enzymatically synthesized by manual or automated reactions. The dsRNA construct may be synthesized by a cellular RNA polymerase or a bacteriophage RNA polymerase (e.g., T3, T7, SP6). The use and production of an expression construct are known in the art 32,33,34 (see also WO 97/32016; U.S. Pat. Nos. 5,593,874, 5,698,425, 5,712,135, 5,789,214, and 5,804,693; and the references cited therein). If synthesized chemically or by in vitro enzymatic synthesis, the RNA may be purified prior to introduction into the cell. For example, RNA can be purified from a mixture by extraction with a solvent or resin, precipitation, electrophoresis, chromatography or a combination thereof. Alternatively, the dsRNA construct may be used with no or a minimum of purification to avoid losses due to sample processing. The dsRNA construct may be dried for storage or dissolved in an aqueous solution. The solution may contain buffers or salts to promote annealing, and/or stabilization of the duplex strands.

[0139] Physical methods of introducing nucleic acids include injection of a solution containing the dsRNA construct, bombardment by particles covered by the dsRNA construct, soaking the cell or organism in a solution of the RNA, or electroporation of cell membranes in the presence of the dsRNA construct. A viral construct packaged into a viral particle would accomplish both efficient introduction of an expression construct into the cell and transcription of dsRNA construct encoded by the expression construct. Other methods known in the art for introducing nucleic acids to cells may be used, such as lipid-mediated carrier transport, chemical mediated transport, such as calcium phosphate, and the like. Thus the dsRNA construct may be introduced along with components that perform one or more of the following activities: enhance RNA uptake by the cell, promote annealing of the duplex strands, stabilize the annealed strands, or other-wise increase inhibition of the target gene.

Abe et al have taught the inhibiting of influenza virus via the use of antisense oligonucleotides targeting various genes of the influenza genome. It has been taught, for example to target the PB1, PB2, PA and NP genes of influenza. Abe et teach the use of liposomes. Abe et al have shown a protective effect of antisense inhibition of influenza in mice that were provided antisense via i.v. administration showing reduced influenza proliferation in lungs, reduced lung damage and increased survival rates. Abe

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et al have therefore demonstrated nucleic acid inhibition as a viable means for protecting against the influenza virus.

Gitlin et al have shown the inhibition of polio virus genes via the use of siRNA compounds. Gitlin et al have shown that siRNA can provide a therapeutic strategy against human viruses. Gitlin et al have also taught that improved strategy of inhibiting or providing cellular immunity to human viruses, especially RNA viruses will have to contend with their variability due to high mutation rates. They teach that using dsRNA directed to multiple conserved RNA target sequences will provide for the aforementioned.

Brummelkamp et al and Paddison et al have both taught the use of vectors utilizing polIII promoters for the effective expression of siRNA and shRNA compounds in vivo.

The art taken as a whole has therefore shown that there is a need in the art to inhibit influenza virus which is well known in the art to be a problem in the human population, for example. The art has shown the inhibition of influenza targeting various influenza genes via antisense compounds where Beach et al and Tuschl et al both teach that siRNA is a more effective and safer means of gene inhibition than antisense and Gitlin et al have demonstrated the inhibition of human viral genes via siRNA. One in the art would clearly have looked to use a more effective compound in the inhibition of influenza. The art has taught that known means of delivery and nucleic acid modifications can be used for/in siRNA compounds. The art has taught that siRNA and shRNA compounds can be delivered via vectors and specifically teaches the use of

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polIII promoters as an effective means of providing siRNA and shRNA compounds. The art has also taught that to better provide protection from viral infection, that multiple conserved regions of the viral genes should be targeted. The prior art also shows that siRNA has the capacity to inhibit gene expression by many fold where the inhibition levels are optimized via siRNA selection, dose, duration and delivery means.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

### ***Response to Arguments***

Applicant's arguments filed 6/24/09 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant has addressed each reference and concludes that none of the references teach/disclose the claimed invention. Applicant does not argue the reasons of record for the combining of the references and does not address that art as a whole. Applicant asserts that Tuschl provides only a very general description of siRNA technology. This opinion is not agreed with. Tuschl provides ample guidance on the design and use of siRNA to inhibit the expression of any gene with a known sequence.

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Applicant provides no argument or evidence to refute the teachings of Tuschl et al.

Tuschl provides ample guidance for the design of siRNA to inhibit any desired target with a known sequence. Applicant does not address the Paddison or Brummelkamp references other than to say they fail to cure deficiencies of other references. Applicant does not argue that Beach et al have provided guidance for expressing siRNA from vectors, only that Beach et al have not taught expression of siRNA targeting a respiratory virus. Abe clearly teaches the inhibition of influenza and clearly provides motivation to inhibit influenza. Applicant again only asserts that Abe does not teach siRNA inhibition of a respiratory virus. Applicant does not refute that Gitlin et al disclose the benefit of targeting conserved regions of a virus, but only assert that Gitlin et al have not shown specifically the targeting of a respiratory virus. It is the examiners position that applicant has only combined the teachings of the prior art in such a way that is clearly suggested by the art. That applicant chose a respiratory virus does not negate the teaching of targeting conserved regions of a virus with siRNA compounds, for example. It is unclear why the general teaching would not apply to respiratory viruses, for example. Applicant has not clearly pointed to any particular feature of their invention that would define over the teachings of the prior art.

***Allowable Subject Matter***

Claims 39-48, 64-69, 94-97, 179-184 and 201 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and the removal of nonelected subject matter.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry  
Primary Examiner  
Art Unit 1635

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